UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/697,995 | 10/30/2003 | Dorothea Reilly | 11669.195USU1 | 7395 |

23552 7590 08/24/2007
MERCHANT & GOULD PC
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

| EXAMINER | |
|---|---|
| CROWDER, CHUN | |
| ART UNIT | PAPER NUMBER |
| 1644 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 08/24/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/697,995 | REILLY ET AL. | |
| | Examiner | Art Unit | |
| | Chun Crowder | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *55,58-68,70-101,103-105,107-113 and 121-132* is/are pending in the application.

4a) Of the above claim(s) *86, 100, 121-129, and 130* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55, 58-68, 70-85, 87-99, 101, 103-105, 107-113, and newly added claims 131, and 132* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/08/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Applicant's amendment to the claims, filed on June 8, 2007, has been entered.

Claims 1-54, 56-57, 69, 102, 106, 114, 115-120 have been canceled.
Claims 121-132 have been added.

Claims 55, 58-68, 70-101, 103-105, 107-113, and 121-132 are pending.

Applicant argues that claim 100 recites a single polynucleotide encodes both DsbA and DsbC, thus, applicant argues that claim 100 encompasses the elected species of DsbA and should not have been withdrawn from consideration.

This is not found persuasive for following reasons:

The originally elected invention including species of a polynucleotide encodes DsbA (see Response to Restriction Requirement mailed on May 5, 2006). Therefore, only claims that encompass the elected inventions and the elected species are currently under consideration. Given that claim 100 encompasses nonelected species of DsbC, claim 100 is drawn to nonelected invention and thus has been withdrawn.

Further, newly added claims 121-129 and 130 are directed to nonelected invention because claims 121-128 are drawn to a method for decreasing aggregation of an immunoglobulin heavy chain and claim 130 is drawn to an eukaryotic host cell. While the elected invention is drawn to a polynucleotide encoding an antibody IgG1, a vector, *E.Coli* host cells, DsbA, and the heavy and light chains are encoded by a single polynucleotide and a method of producing the antibody. These inventions differ because the methods differ with respect to one or more of ingredients, method steps, and/or endpoints; therefore, each method is patentably distinct.

Furthermore, the distinct ingredients, method steps, and/or endpoints require separate and distinct searches. As such, it would be burdensome to search these Inventions together. Furthermore, the species of prokaryotic and eukaryotic host cells are distinct because they differ in structures, physicochemical properties and mode of action. There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by the original presentation for prosecution on the merits. Accordingly, claims 121-128 and 130 have been withdrawn from consideration as being directed to a nonelected species. See 37 C.F.R. 1.142(b).

Claims 86, 100, 121-129, and 130, have been withdrawn from consideration, under 37 C.F.R. 1.142(b), as being drawn to nonelected inventions.

Claims 55, 58-68, 70-85, 87-99, 101, 103-105, 107-113, and newly added claims 131, and 132 are currently under consideration as they read on the originally elected invention of a polynucleotide encoding an antibody IgG1, a vector, *E.Coli* host cells, DsbA, and the heavy and light chains are encoded by a single polynucleotide and a method of producing the antibody.

2. This Office Action will be in response to applicant's arguments, filed on June 8, 2007.

The rejections of record can be found in the previous Office Action, mailed on June 30, 2006 and January 8, 2007.

3. In light of applicant's amendment to the claims, the previous objection and rejection under 35 U.S.C. 112, 1st paragraph, written description, have been withdrawn.

4. Claim 132 is objected to because it depends on non-elected claims. Applicant should amend the claim as independent from non-elected claims. Appropriate correction is required.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. This is a **New Ground of Rejection**. Claims 55, 58-68, 70-85, 87-99, 101, 103-105, 107-113, and newly added claims 131, and 132 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a *Written Description*, New Matter rejection.

The phrase "wherein the cysteine residue forms an inter-chain disulfide linkage when present" are not supported by the original disclosure or claim as filed.

Applicant's amendment, filed on June 8, 2007, directs to support to pages 4, 5, and 35, and asserts that no new matter has been added.

However, the specification as filed does not provide sufficient written description of the above-mentioned "limitations". The specification does not provide sufficient support for an isolated polynucleotide encoding an intact antibody comprising a variant heavy chain with a hinge region lacks a cysteine residue wherein the cysteine residue forms an inter-chain disulfide linkage when present.

The specification only disclose an isolated polynucleotide encoding an intact antibody comprising a variant heavy chain with a hinge region lacks a cysteine residue wherein the cysteine residue is capable of forming disulfide linkage when present; the instant claims now recite an isolated polynucleotide, which were not clearly disclosed in the specification. Therefore, the claims represent a departure from the specification and claims originally filed. Applicant's reliance on the disclosure of cysteine residues capable of forming disulfide linkage does not provide sufficient direction and guidance to the features currently claimed ("wherein the cysteine residue forms an inter-chain disulfide linkage when present"). It is noted that a generic or a sbu-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679 683 (CCPA 1972) and MPEP 2163.05.

Such limitation recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action.

Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above. See MPEP 714.02, 2163.05-06 and 2173.05 (i).

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 55 and 58 stand rejected under **35 U.S.C. 102(b)** as being anticipated by Gillies et al. (Human Antibody Hybridomas. 1990 1;1:47-54. Cited on IDS filed 05/02/2006) and Davis et al. (The EMBO Journal 1989. 8;9:2519-2526. Reference cited on IDS filed 06/25/2004) for reasons of record set forth in the previous Office Actions mailed on June 30, 2006 and January 8, 2007.

Applicant's arguments have been fully considered but have not been found persuasive.

It is noted only claims 55 and 58 have been rejected herein. The rejection does not apply to claims 59-85, 87-99, 101, and 103-114 as applicant indicated in the Remarks filed on June 8, 2007 (see page 14 of the Remarks).

Applicant argues that Gillies et al. do not teach polynucleotide encoding an intact antibody; applicant asserts that the teachings of Gillies et al. encompass only a construct encoding the heavy chain variable domain and the CH1 domain. Therefore, applicant argues Gilles et al. do not anticipate the claimed invention.

This is not found persuasive for following reasons:

Contrary to applicant's assertion that Gillies only teach truncated antibody not the intact antibody, it is noted that a prior art reference must be considered in its entirety, MPEP 2141.02.

In this case, Gillies et al. teach an isolated polynucleotide encoding both CH1 deleted antibody and an intact antibody comprising a variant heavy chain wherein the variant heavy chain comprises a hinge region which does not form inter-heavy chin disulfide linkages because the heavy chain hinge region carries mutations of the two cysteine residues (see Abstract on page 47, Materials and methods on pages 48-49 and Results on pages 50-52). Thus, Gillies et al. anticipates the claimed invention.

Further, applicant argues that Davis et al. teach only IgM variant and it is well known in the art that IgM lacks a hinge region; thus applicant argues that the teachings of Davis et al. does not meet the claimed limitation of "variant hinge region".

This is not found persuasive for following reasons:

Contrary to applicant's assertion, it is noted that the instant claims do not exclude IgM antibody. It is noted that during patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification". See MPEP 2111. In this case, the instant specification would contradict applicant's argument because the disclosure states "IgM and IgD lack a hinge region, but each contains an extra heavy chain domain; at least one (in some embodiment, all) of the cysteines of the heavy chain can be rendered incapable of disulfide linkage formation in the methods of the invention"(see page 29 of the instant specification, in particular). Thus, the reference teachings would read onto the claimed invention when the claims are given the broadest reasonable interpretation consistent with the specification.

Therefore, applicant's arguments have not been found persuasive.

9. Claims 55, 58-68, 70-85, 87-99, 101, 103-105, 107-113, and newly added claims 131, and 132 are rejected under **35 U.S.C. 102(e)** as being anticipated by Simmons et al. (US Patent Application 2005/0170464) for reasons of record set forth in the previous Office Actions mailed on June 30, 2006 and January 8, 2007.

Applicant's arguments have been fully considered but have not been found persuasive.

Applicant argues that Simmons et al. teach that only those cysteine residues not involved in maintaining the proper structures of an antibody can be substituted. Applicant further argues that the reference does not teach an intact antibody wherein the variant heavy chain comprises a variant hinge region which dose not form inter-heavy chain disulfide linkages and wherein said variant hinge region lacks a cysteine that forms an inter-chain disulfide linkage. Further, applicant asserts that Simmons et al. do not teach aggregation of heavy chains and that alteration of hinge cysteines can affect the aggregation and improve the yield of an antibody.

This is not found persuasive for following reasons:

Contrary to applicant's assertion that Simmons et al. fail to teach each and every element of the claims, the examiner acknowledges that a generic chemical formula will anticipate a claimed species covered by the formula when the species can be "at once envisaged" from the formula; If one of ordinary skill in the art is able to "at once envisage" the specific compound within the generic chemical formula, the compound is anticipated. See MPEP 2131.02.

Here, given that Simmons et al. specifically teach that the antibodies or immunocojugates can be variants with amino acid substitutions in the Fc regions and any cysteine residue may be substituted with serine to improve the oxidative stability and prevent aberrant crosslinking (e.g. see pages 12-15) and the limited number of cysteine residues in an antibody, one skill artisan would immediately envisage that Simmons et al. taught the amino acid substitution from cysteine to serine in the Fc region including the those cysteine residues in the hinge region that are responsible forming inter-heavy chain disulfide bonds. Further, Simmons et al. teach isolated polynucleotide encoding an antibody in a prokaryotic vector comprising a promoter and secretion signal sequence (see Figures 7 and 9, in particular).

Regarding applicant's assertion that the reference does not teach aggregation of heavy chains and that alteration of hinge cysteines can affect the aggregation and improve the yield of an antibody, it is noted that the reduction in aggregation of antibody and the improvement in yield would be inherent properties of the referenced methods.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Therefore, the reference teachings anticipate the claimed invention. Applicant's arguments have not been found persuasive.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 55, 58-68, 70-85, 87-99, 101, 103-105, 107-113, and newly added claims 131, and 132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gillies et al. (Human Antibody Hybridomas. 1990 1;1:47-54. Cited on IDS filed 05/02/2006) and Davis et al. (The EMBO Journal 1989. 8;9:2519-2526. Reference cited on IDS filed 06/25/2004) in view of Georgiou et al. (US Patent 5,264,365. Reference cited on IDS filed 10/20/2004) and Kurokawa et al. (The Journal of Biological Chemistry. 2001. 276;17:14393-14399) for reasons of record.

Applicant's arguments have been fully considered but have not been found persuasive.

Applicant's arguments and the Examiner's rebuttal regarding the teachings of Gillies et al. and Davise et al. are essentially the same as discussed above in Section 9.

Applicant further argues that none of these references when combined teach or suggest a polynucleotide encoding an intact antibody comprising a variant heavy chain wherein the variant heavy chain comprises a variant hinge region that does not form inter-heavy chain disulfide linkage.

This is not found persuasive for following reasons:

The Office Action mailed on June 30, 2006 states:

*"The teachings of Gillies et al. and Davis et al. have been discussed, supra.*

*The reference teachings differ from the claimed invention by not describing E.Coli host cells with DsbA and deficient in endogenous protease activities.*

*However, methods of making heterologous proteins using modified prokaryotic host cell such as certain E.Coli strains were well known in the art at the time the invention was made. For example, Georgiou et al. teach methods of making recombinant proteins using protease deficient E.Coli strain (see entire document, particularly Summary of the Invention on columns 2-6). Georgiou et al. further teach using E.Coli strain deficient in proteases as host cells for producing recombinant protease sensitive proteins such as antibody fragment provides inexpensive ways of producing recombinant proteins in large quantity, correct folding, and reduced protein degradation (e.g. see columns 1-2, in particular).*

*Kurokawa et al. teach that the periplasm of E.Coli contains enzymes that can assist protein folding such as disulfide bond formation proteins Dsb and over-expression of Dsb proteins can increase efficiency of periplasmic expression of heterologous proteins with multiple disulfide bonds in E.Coli (see entire document, particularly pages 14393-14394).*

*It would thus have been obvious to the ordinary artisan at the time the invention was made to make antibody comprising a variant heavy chin hinge region incapable of inter-heavy chain disulfide linkage using E.Coli strain with Dsb proteins and deficient in proteases. The ordinary artisan would have been motivated to produce the antibody variant using E.Coli strain expressing Dsb proteins and deficient in proteases because Dsb proteins can increase efficiency of periplasmic expression of heterologous proteins with multiple disulfide bonds and E.Coli strain deficient in proteases can provide inexpensive ways of producing recombinant proteins in large quantity, correct folding, and reduced protein degradation.*

*Given the teachings of Gillies et al. and Davis et al. regarding methods of making antibody variant incapable of forming inter-heavy chain disulfide linkage, and the teachings of Georgiou et al. and Kurokawa et al. providing methods of making antibody using E. Coli strains with Dsb proteins and deficient in proteases, the ordinary artisan at the time the invention was made would have had a reasonable expectation of success of producing antibody variant incapable of inter-heavy chain disulfide linkage formation using E. Coli strains with Dsb proteins and deficient in proteases.*

*Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary."*

In contrast to applicant's assertion that there is not motivation to combine the teachings of the references, it is noted that all of the claimed elements including an isolated polypeptide encoding an intact antibody comprising an variant hinge region which does not form inter-heavy chain disulfide linkages wherein said variant hinge region lacks a cysteine residue, E.Coli host cells with DsbA and deficient in endogenous protease activities, as well as prokaryotic host cells and method of producing an intact antibody were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions and the combination would have yield predictable results.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have not been found persuasive.

12. Conclusion: no claim is allowed.

13. Applicant's request for interview, filed on June 8, 2007, is acknowledged. This Office Action is sent in a timely manner due to the administrative procedures. Applicant is encouraged to contact the Examiner to arrange an interview if still deemed appropriate after receiving this Office Action.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chun Crowder whose telephone number is (571) 272-8142. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chun Crowder, Ph.D.
Patent Examiner
August 20, 2007

Maher M. Haddad
MAHER M. HADDAD
PRIMARY EXAMINER